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## Mechanisms Behind Intracoronary Radiation Therapy Failure

We read with great interest the study by Ajani et al., "The Outcome of Percutaneous Coronary Intervention in Patients With In-Stent Restenosis Who Failed Intracoronary Radiation Therapy" (1). Limited data are available on the outcomes of patients with in-stent restenosis (ISR) who undergo treatment using intracoronary radiation therapy (IRT) and subsequently "fail," and the study by Ajani and colleagues provides new data on this important subject. The investigators reported that the rate of failed IRT was 29%. This is similar to findings from our institution where we reported a 15.6% failure rate after IRT for ISR in a broad range of patients (2). In our study, ostial location and smaller postprocedural minimal luminal diameter were correlated with subsequent failure after IRT. Do the investigators of this current study have information regarding the effects of these factors on influencing long-term clinical outcomes in their patient cohort?

In this current study, cutting balloon angioplasty (CBA) was utilized in only 2% of cases after failed IRT. Because of the potential for minimizing arterial injury, reducing the proliferative neointimal response, achieving a greater postprocedural minimal luminal diameter, and decreasing slippage due to "watermelon seeding," CBA has been shown to be a safe and feasible strategy for the treatment of ISR (3); however, the impact of CBA in combination with IRT for the treatment of ISR has not been well established. We recently reported data from our institution which showed that the strategy of CBA and IRT using Sr-90 for ISR was associated with similar major adverse cardiac events (death, myocardial infarction, and target vessel revascularization) at 6 months compared to percutaneous transluminal coronary angioplasty (PTCA) and IRT in 102 consecutive patients (20.0% vs. 29.8%, $p = 0.36$) (4). Thus, although CBA has the potential of avoiding geographic miss by limiting the mismatch between the injured and irradiated arterial segments, it does not appear to offer any clinical advantage over conventional balloon angioplasty in combination with IRT, although further studies are needed to clarify this issue. The mechanism behind this observed lack of benefit for the treatment of ISR may be that, although CBA appears to increase neointimal tissue extrusion, intravascular ultrasound studies have shown that CBA, unlike PTCA, is associated with minimal stent overexpansion (5).

The majority of the patients in the current study presented with a focal pattern of restenosis. Did the clinical presentation of these patients differ from those who presented with diffuse or edge restenosis?

In the study by Ajani et al. (1), the mean time to first target vessel revascularization (TVR) was 173 ± 127 days after the index procedure. Other studies have noted that in patients who "fail" IRT, treatment with brachytherapy delays the time to the first TVR (295 ± 206 days) compared to the placebo group (202 ± 167 days) ($p = 0.03$) (6). Preliminary data from our medical center suggests that up to 25% of patients who ultimately "fail" IRT present more than eight months after the index treatment, and in these patients the mean duration to TVR was 14.2 ± 3.7 months (7). Do the investigators of the current study (1) have data on patients who failed IRT and who presented beyond the traditional time period for restenosis (six to nine months)?

Although glycoprotein IIb/IIIa inhibitors (GPI) have been shown to be beneficial in a wide variety of coronary interventional procedures, the impact of these agents on improving outcomes in patients with ISR using IRT is not clearly defined. One study showed that the utilization of GPI in conjunction with IRT for ISR was associated with similar death, myocardial infarction, and TVR compared to IRT without GPI (19.5% vs. 23.7%, $p = 0.511$) (8). What was the rate of utilization of GPI in the current study, and did this influence the outcome?

The study by Ajani and co-workers contributes greatly to our understanding of the issues surrounding the optimal implementation of IRT in this high-risk population. Assessing the risk for IRT failure and elucidating the mechanisms underlying these adverse events will contribute significantly to the application of IRT for ISR in the drug-eluting stent era.

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## REPLY

We thank Drs. Almeda and Schaer for their interesting comments. We have previously reported that ostial in-stent restenotic lesions treated with intracoronary radiation have equivalent clinical outcomes to nonostial irradiated in-stent restenotic lesions and have significantly reduced recurrent restenosis compared to in-stent restenotic ostial lesions treated with conventional percutaneous interevention alone (1). We did not find that postprocedural minimal luminal diameter correlated with subsequent failure, although smaller vessels (based on reference vessel diameter) have higher restenosis rates. Intracoronary radiation therapy reduces angiographic restenosis in all sized vessels, with the effect seen predominantly in small vessels (<2.5 mm) (2). In the current analysis, these factors did not influence clinical outcomes.

The initial enthusiasm for the cutting balloon as an interventional strategy for in-stent restenosis has not been supported by reduced event rates in clinical trials. There is no evidence showing the cutting balloon to be superior over conventional angioplasty with adjunctive intracoronary radiation.

Our ongoing analysis suggests the time to first target vessel revascularization in the majority of patients is between 6 to 12 months, suggesting there is a "delay" in recurrent restenosis compared to conventional angioplasty. Recurrent restenosis beyond 12 months has been infrequent in the majority of published Washington Radiation for In-stent restenosis Trial (WRIST) series.

The overall use of glycoprotein (GP) IIb/IIIa inhibitors in the current analysis was 22% and did not influence clinical outcomes. Integrilin WRIST was a randomized trial addressing whether the treatment of eptifibatide (small-molecule competitive GPIIb/IIIa inhibitor) would improve both the procedural and the long-term outcomes in patients undergoing treatment for in-stent restenosis with intracoronary radiation therapy. That study (submitted for publication) did not detect differences in major clinical events with use of GPIIb/IIIa inhibitors. However, at any end point of the study there was nonsignificant reduction of creatine phosphokinase release in the eptifibatide group when compared to control, and these findings may stimulate a larger study to detect benefit of GPIIb/IIIa inhibitors in the setting of intracoronary radiation therapy.

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## Clinical Decision Making on Statin Drug Interactions

Recent comments by Dr. Hansten (1) regarding drug-drug interactions and myopathy risk with statins provide important additional information to guidelines issued last year on the use of these agents (2). The metabolism of statins is complex, with extensive conversion between the lactone, open-acid, and glucuronidated forms as well as other less common metabolites (3,4). As Dr. Hansten noted, pravastatin undergoes the least cytochrome P450 (CYP)-mediated metabolism and is therefore the least susceptible to interactions with drugs that inhibit this system (5–7). Also, simvastatin and lovastatin are more prone to interactions with CYP inhibitors, owing in part to the fact that these agents are administered as the more lipophilic lactone form, whereas all other agents (including cerivastatin) are administered as the open-acid form (3,8). And though these findings are important, I believe they should be incorporated into clinical practice with several important caveats in mind.

First, the kinetics of statins is more complex than just their hepatic handling. The 5-fold increase in pravastatin area under the curve (AUC) induced by cyclosporine is now widely recognized to be the result of inhibition of the adenosine triphosphate-binding cassette transporter P-glycoprotein (Pgp) in the gut wall (9,10). Inhibition of Pgp allows greater absorption of pravastatin, thereby increasing its systemic bioavailability, which is already four-fold higher than lovastatin and simvastatin (3,8). Other inhibitors of Pgp include erythromycin, quinidine, amiodarone, and verapamil (11–13).

Second, the greatest risk of myopathy with statins occurs when they are used with other lipid-lowering agents and is the result of pharmacodynamic, as well as pharmacokinetic, interactions (3,8,10,14). In this regard, pravastatin carries an increased risk similar to the other agents (5,15,16). And though case reports of myopathy are more common with lovastatin and simvastatin, four published studies of 39,285 patients and over 160,000 patient-years of therapy have failed to find a greater risk for these agents compared to placebo (14,17,18).

Finally, the primary aim of statins is to reduce cardiovascular (CV) events. The recent failure of 40 mg of pravastatin to significantly reduce CV events in the ALLHAT-LLT trial (19) stands in contrast to the recent findings of a robust benefit of 40 mg of simvastatin in the HPS trial (17). It is also notable that while a lower threshold low density lipoprotein (LDL) of 125 mg/dl was found for the beneficial effects of pravastatin in both the CARE and LIPID trials (20,21), no such threshold finding for simvastatin was found in the 4S trial (18). In fact, in the HPS trial, CV events were significantly reduced by simvastatin in the 3,500 participants with a baseline LDL below 100 mg/dl (mean 97 mg/dl) (17).

Thus, though interactions should always be considered when prescribing multiple medications, until clearer mechanisms of both benefit and risk are elucidated for statins, outcomes data remain